Temporal Artery Biopsy for Giant Cell Arteritis

REGINA TAYLOR-GJEVRE, MINH VO, DINO SHUKLA, and LOTHAR RESCH

ABSTRACT. ***Objective.*** To evaluate the influence of temporal artery biopsy (TAB) techniques on establishing a diagnosis of giant cell arteritis (GCA).

Methods. A retrospective review of 141 TAB pathology records from 1996 to 2002 was conducted. Histopathology slides on 136 TAB were reviewed by a single, independent, blinded pathologist.

Results. The population included 101 (71.6%) women, mean age 75.8 years (range 45–92), and 40 men, mean age 73.9 years (range 47–90). The mean length of a TAB sample after formalin fixation was 1.76 cm (range 0.1–5.3). Surgeons performing the TAB represented 6 disciplines. Ophthalmologists had the largest volume, at 78 biopsies (55.3%), and the longest segments of artery, with a mean length of 2.37 cm (range 0.4–5.3) ($p < 0.001$). Comparison of biopsy interpretation provided a kappa coefficient of 0.8 (95% CI 0.69, 0.91). The 38 (27%) positive biopsies had a mean length of 2.07 cm (SD 1.1), and the 98 negative biopsies a mean length of 1.69 cm (SD 1.04) ($p = 0.058$). Biopsies < 1.0 cm length (n = 35, 25.7%) were less likely to be positive than those ≥ 1.0 cm ($p = 0.037$). No significant differences in surgical discipline, hospital site, number of slides, or cross-sections/cm artery were found between the positive and negative biopsies.

Conclusion. Biopsy specimens reported positive for GCA tended to be longer than those reported as negative. A "threshold" size of 1.0 cm is associated with increased diagnostic yield. Lack of standardization of biopsy harvesting and processing techniques may contribute to variable sensitivity of TAB. (J Rheumatol 2005;32:1279–82)

Key Indexing Terms:
TEMPORAL ARTERITIS GIANT CELL ARTERITIS BIOPSY SENSITIVITY

Giant cell arteritis (GCA) or temporal arteritis is a vasculitis affecting large and medium size arteries in patients over 50 years of age. Diagnosis is facilitated by the presence of characteristic histopathology on temporal artery biopsy (TAB)[1]. There is regional variation in reported incidence of GCA[2]. The sensitivity of TAB may vary depending on the pretest probability of the population and the clinical threshold for considering the procedure. The clinical features of constitutional symptoms, abnormal temporal artery on physical examination, and the presence of visual complications have been associated with higher odds of a positive biopsy for temporal arteritis[3]. The false-negative biopsy rate, utilizing the American College of Rheumatology 1990 criteria for the classification of GCA, has been reported to be 15.3%–38.9%[4]. Complicating the diagnostic sensitivity of TAB is the potentially discontinuous character of the histopathological changes. Skip lesions have been reported in 28%[5]. To minimize false-negative results, guidelines for optimal length of artery excised have been proposed, which vary from 2 to 7 cm[5-7].

When GCA is suspected clinically, treatment is often initiated before the results of the biopsy are known. However, depending on the clinical index of suspicion, substantial diagnostic weight may be placed on the biopsy result. Variability in sampling, preparative techniques, and/or histopathological interpretation may contribute to inconsistent diagnostic sensitivity of TAB. We investigated the influence of biopsy techniques on establishing a diagnosis of temporal arteritis in our center.

MATERIALS AND METHODS

Pathology records from 1996 to 2002 from all 3 Saskatoon hospitals (Royal University Hospital, Saskatoon City Hospital, and St. Paul's Hospital) were retrospectively reviewed. During this period, 141 TAB were performed in patients with suspected GCA. The following information was recorded for each case: age, sex, length of biopsy (after formalin fixation), surgeon's subspecialty, hospital site, pathologist, and the reported biopsy result (positive or negative). Gross biopsy sectioning and pathologic interpretation was consistently performed at the original TAB hospital site; however, in 2000, central slide preparation was initiated. Tissue processing was cross-sectional in contrast to longitudinal. Cross-sections of 5 µm thickness were prepared by microtome.

Slides were subsequently reviewed and reported as positive or negative, by an independent anatomic pathologist (LR), who was blinded to the original reported result. Data on number of slides and number of cross-sections/slide was obtained. These data were correlated with length of TAB to determine the number of slides and cross-sections/cm of arterial segment.

For pathologic diagnosis, temporal arteritis was defined as: inflammation of the wall of the temporal artery comprising lymphocytes, epithelioid histiocytes, and frequently multinucleated giant cells, involving to at least some extent the internal elastic lamina with frequent fragmentation of the same[8].

From the Division of Rheumatology, Department of Medicine, and the Department of Internal Medicine, University of Saskatchewan, Saskatoon, Saskatchewan; and the Department of Pathology, University of Alberta, Edmonton, Alberta, Canada.

R.M. Taylor-Gjevre, MD, FRCPC, Division of Rheumatology; M. Vo, MD; D. Shukla, MD, Department of Internal Medicine, University of Saskatchewan; L. Resch, MD, FRCPC, Department of Pathology, University of Alberta.

Address reprint requests to Dr. R.M. Taylor-Gjevre, Division of Rheumatology, Department of Medicine, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada.

Accepted for publication February 21, 2005.

Statistical analysis. SPSS v. 12.0 was employed for data entry and analysis. Two-group comparisons of biopsy length were analyzed by both 2-tailed Student t tests and nonparametric analysis (Mann-Whitney U test). ANOVA was utilized for 3 or more group comparisons. Frequency data were analyzed by chi-square testing and Fisher's exact test when the expected cell count was less than 5. Kappa coefficient was employed to assess interobserver agreement[9].

RESULTS

During 1996–2002, unilateral TAB were performed on 141 patients. The mean age of these patients was 75.2 years (range 45–92). The population included 101 women (71.6%) with a mean age of 75.8 years (range 45–92). The men had a mean age of 73.9 years (range 47–90).

Operating surgeons represented 6 different disciplines, including ophthalmology, plastic surgery, general surgery, neurosurgery, vascular surgery, and family medicine. Ophthalmologic surgeons performed 78 biopsies (55.3%), plastic surgeons 32 biopsies (22.7%), and other disciplines each performed less than 10% of biopsies. No statistically significant differences in frequency of positive biopsies were noted between surgical disciplines (Table 1).

Based on recorded length of biopsied artery segments (post-formalin fixation), the mean length was 1.76 cm (range 0.1–5.3; median 1.7; mode 2.0 cm). Significant differences were found in biopsy length among the surgical disciplines. Ophthalmologists harvested significantly longer temporal artery segments, with a mean length of 2.37 cm (range 0.4–5.3; $p < 0.001$).

The group of pathologists originally providing interpretation of the 141 biopsy specimens was relatively large at 24. The number of biopsies in this sample reviewed by an individual pathologist ranged from one to 39. Based on this multiple-observer analysis, the biopsy specimens interpreted as positive had a mean length of 1.84 cm (SD 1.08) and the negative, 1.72 cm (SD 1.06). This was not a statistically significant difference in length ($p = 0.523$).

In all but 5 cases, slides could be retrieved for blinded independent single-observer pathology review. The kappa coefficient for comparison between the original pathology interpretation and the blinded independent pathology interpretation was 0.8 (95% CI 0.69, 0.91).

In the independent blinded review of pathology slides, a diagnosis of GCA was made on 38 (27%) biopsy specimens, and 98 specimens were negative. The mean length of the positive specimens was 2.07 cm (SD 1.1), and of the negative specimens 1.69 cm (SD 1.04; Figure 1). This difference approached statistical significance ($p = 0.058$, 95% CI –0.786, 0.014, by Student t test; $p = 0.054$ by Mann-Whitney U test). Total number of slides, number of slides/cm artery biopsied, number of cross-sections/slide, number of cross-sections/cm artery, and total cross-sections examined/specimen was compared between positive and negative biopsies (Table 2). No significant differences were noted after adjustment for multiple comparisons. Entertaining the possibility of a "threshold" length desirable for pathologic processing and interpretation, TAB data were divided into 2 groups: those < 1.0 cm length (25.7%), and those ≥ 1.0 cm length (74.3%). A cutoff point of 1.0 cm was chosen as the point at which the relationship between TAB length and cumulative percentage of positive biopsies assumes a steeper slope, as illustrated in Figure 2. The biopsies ≥ 1.0 cm length were more likely to be positive than those < 1.0 cm ($p = 0.037$). The biopsies < 1.0 cm included 30 negative biopsies and 5 positive. The longer biopsies included 68 negative and 33 positive specimens. Raising the threshold length above 1.0 cm did not increase the frequency of positive results in the longer specimen group.

Of the 5 irretrievable cases, 3 were originally reported as positive, with a mean length of 1.13 cm (SD 0.47). The 2 cases reported as negative had a mean length of 0.6 cm (SD 0.14).

No significant difference in frequency of a positive biopsy report by blinded pathology review was noted between hospital sites.

DISCUSSION

There is variability in the perception of the role of temporal artery biopsy in the diagnosis of GCA. A substantial false-negative rate does diminish the reliability of a negative report. Conversely, a positive biopsy helps to prevent future doubts about the accuracy of the diagnosis, particularly in the situation of corticosteroid induced adverse events.

Table 1. Comparison of surgical discipline.

Surgical Discipline	No. of Biopsies (N = 141), n (%)	Mean Length, cm (SD)	No. Positive for GCA by Original Report (N = 141), n (%)	No. Positive for GCA by Blinded Review (N = 136), n (%)
Ophthalmology	78 (55.3)	2.37 (0.97)†	31/78 (39.7)	26/77 (33.8)
Plastic surgery	32 (22.7)	1.01 (0.46)	8/32 (25)	4/28 (14)
Neurosurgery	12 (8.5)	1.43 (0.64)	8/12 (67)	4/12 (33)
General surgery	10 (7.1)	0.74 (0.73)	4/10 (40)	2/10 (20)
Vascular surgery	6 (4.3)	0.73 (0.60)	2/6 (33)	2/6 (33)
Family practice	3 (2.1)	0.77 (0.31)	0/3 (0)	0/3 (0)

† $p < 0.001$.

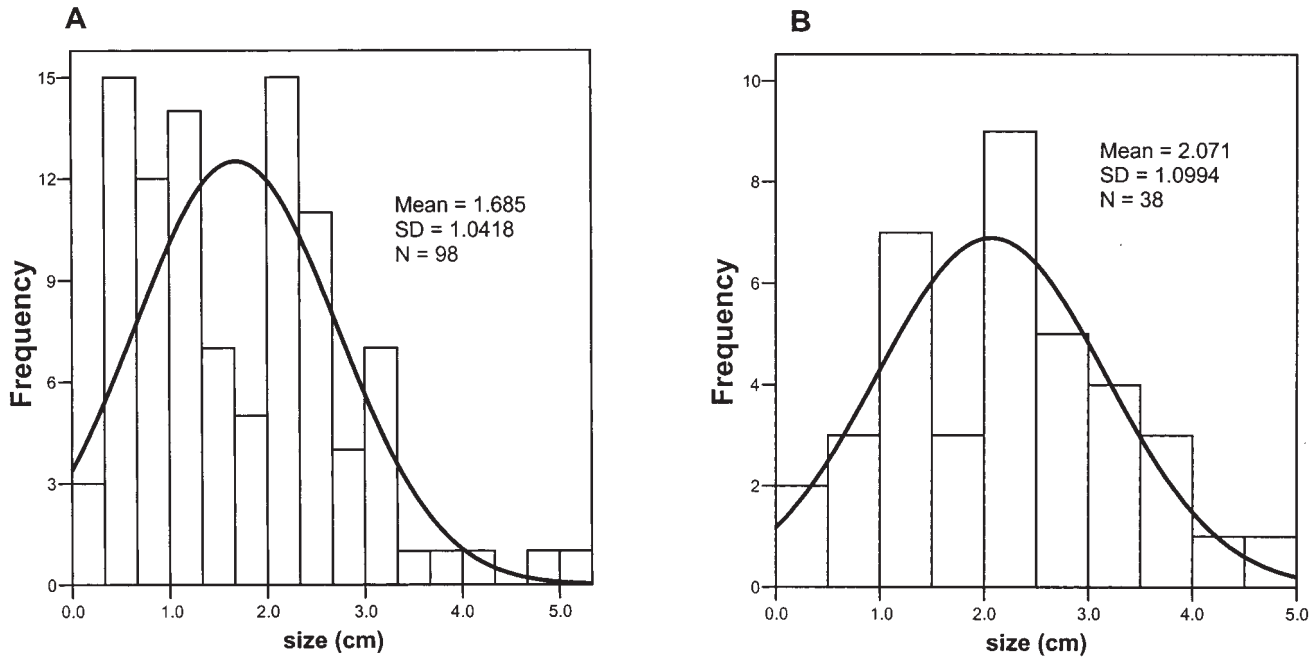

Figure 1. Size distributions of temporal artery biopsies: pathologist's blinded interpretations, (A) negative, (B) positive.

Table 2. Comparison of GCA positive and negative specimens (blinded reviewer).

	GCA Positive, n = 38	GCA Negative n = 98	Significance p
Mean biopsy length, cm (SD)	2.07 (1.1)	1.69 (1.04)	0.058
Mean no. slides/specimen (SD)	4.5 (2.6)	4.9 (2.5)	0.405
Mean no. slides/cm biopsy length (SD)	3.16 (3.61)	4.69 (5.02)	0.088
Mean no. cross-sections/slide (SD)	5.0 (1.9)	4.5 (1.5)	0.111
Mean no. cross-sections/cm biopsy length (SD)	12.03 (7.51)	17.83 (16.86)	0.043*
Mean no. total cross-sections/specimen (SD)	22.3 (15.25)	21.6 (11.4)	0.767

* Not significant when corrected for multiple comparisons.

Initiation of corticosteroids upon clinical suspicion of a diagnosis of GCA is usual procedure, generally prior to scheduled biopsy of one or both temporal arteries. In the situation of high pretest index of suspicion, a negative pathology report does not change clinical management. When the clinical picture is less classic, a negative biopsy report may tip the scales against initiation or continuation of corticosteroid therapy. An evaluation of the need for high-dose corticosteroid therapy in the Olmsted County (Minnesota, USA) GCA population showed TAB had a positive predictive value of 94%[10].

The sensitivity of TAB in diagnosing GCA is not clear. Clinical utility is influenced by the incidence of disease in the population tested, the alacrity with which the procedure is employed, and the vagaries of the disease process itself. Skip lesions, inflammatory lesions in the arterial wall interspersed with normal segments of artery, are not uncommon. Some foci of inflammation have been documented as small as 330 μm[5]. The length of artery segment available for pathology review may be key in making a pathological diagnosis of GCA. Longer segments would be expected to increase the sensitivity of the test. Accordingly, suggestions have been made by several authorities for optimal length of biopsy ranging from 2 to 7 cm[1,5-7]. Kent and Thomas report an institutional increase in mean length of TAB from 0.4 cm in 1980 to 2.4 cm in 1984, with a corresponding rise of 17% in positive biopsies[7]. In another review of 200 TAB with a median length of 1.0 cm, biopsies positive for GCA were significantly longer than negative biopsies[11]. Other investigators have compared biopsy length between GCA positive and negative specimens with opposite findings. Roth, *et al* reported a mean biopsy length from TAB-positive GCA patients of 1.2 cm, in "biopsy-negative" GCA patients of 1.7 cm, and non-GCA patients (true negatives) of 1.5 cm[4]. Chakrabarty and Franks reported GCA-positive biopsies were a median length of 0.9 cm, and negative biopsies a median length of 1.0 cm[12] in their series.

In this study, we initially examined differences in length

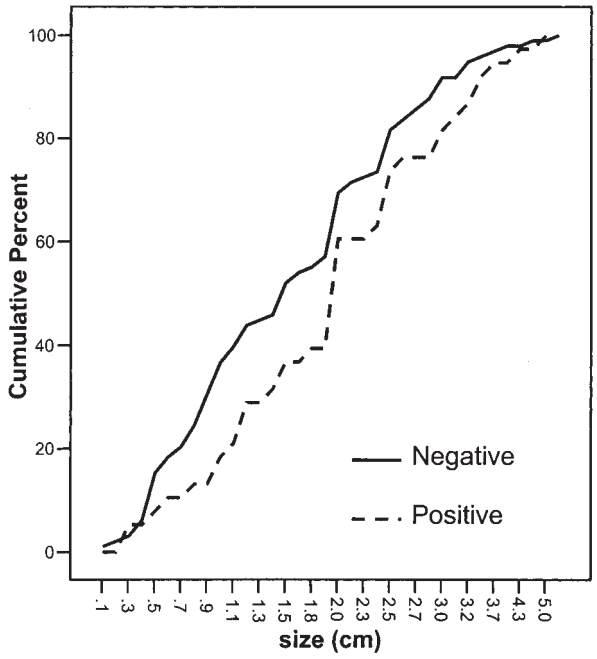

Figure 2. Temporal artery biopsy sizes for negative and positive specimens; interpretations by a blinded pathologist.

of biopsy between cases reported as positive and negative for GCA. No difference was perceived. Review of the histopathology slides by a single, blinded, independent pathologist was then performed. Biopsies were again reported as positive or negative for GCA based on histopathological criteria. The positive biopsies were longer than the negative biopsies. The 0.4 cm difference in mean length between these groups approached but did not reach statistical significance. We considered the possibility of a "threshold" length below which a specimen may be either inadequate due to patchy disease, or technically more difficult to process and therefore to interpret. To evaluate this possibility, TAB < 1.0 cm (n = 35, 25.7%) and those ≥ 1.0 cm were compared. A significantly higher frequency of positive biopsies was observed in the latter group. Raising the minimum threshold length did not result in higher diagnostic yield.

It was apparent that there were differences in length of artery segment harvested between surgical disciplines. Although having no higher proportional diagnostic yield, the ophthalmologic surgeons both did the most biopsies of any of the 6 surgical categories, and as well harvested the longest specimens. There was a substantial range in the length of the biopsy harvested, between 0.1 cm and 5.3 cm. It should be pointed out that these lengths were measured after formalin fixation, which does cause tissue shrinkage. Positive biopsies did not have greater numbers of slides and cross-sections examined compared to the negative specimens. This is consistent with Chakrabarty and Franks' findings that routine examination of TAB at multiple levels does not increase the diagnostic yield of the test[12].

Our study was a retrospective review of pathology records and slides. Positive TAB tended to be longer than negative biopsies. From our data a threshold length of 1.0 cm of arterial segment after formalin fixation would appear to increase the diagnostic yield of TAB. We recommend harvesting a minimum TAB length of 1.5 cm, in order to allow for tissue shrinkage with fixation, which has been estimated to approximate 10%[13]. Close communication with our surgical colleagues is essential before biopsy.

REFERENCES

1. Lie JT. Temporal artery biopsy diagnosis of giant cell arteritis: lessons from 1109 biopsies. Anat Pathol 1996;1:69-97.
2. Silman AJ. Polymyalgia rheumatica and giant cell arteritis. In: Silman AJ, Hochberg MC, editors. Epidemiology of the rheumatic diseases. 2nd ed. New York: Oxford University Press; 2001:188-204.
3. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, Gonzalez-Louzao, Rodriguez-Ledo P. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. Semin Arthritis Rheum 2001;30:249-56.
4. Roth AM, Milsow L, Keltner JL. The ultimate diagnoses of patients undergoing temporal artery biopsies. Arch Ophthalmol 1984;102:901-3.
5. Klein RG, Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. Mayo Clin Proc 1979;51:504-10.
6. Gordon LK, Levin LA. Visual loss in giant cell arteritis. JAMA 1998;280:385-6.
7. Kent RB 3rd, Thomas L. Temporal artery biopsy. Am Surg 1990;56:16-21.
8. Kalimo H, Kaste M, Haltia M. Vascular diseases. In: Graham DI, Lantos PL, editors. Greenfield's neuropathology. 7th ed. London: Arnold Publishers/Oxford University Press; 2002:298.
9. Rigby AS. Statistical methods in epidemiology. V. Towards an understanding of the kappa coefficient. Disabil Rehabil 2000;22:339-44.
10. Hall S, Persellin S, Lie JT, O'Brien PC, Kurland LT, Hunder GG. The therapeutic impact of temporal artery biopsy. Lancet 1983;2:1217-20.
11. Sudlow C. Sensitivity of temporal artery biopsy varies with biopsy length and sectioning strategy [letter]. BMJ 1997;315:549.
12. Chakrabarty A, Franks AJ. Temporal artery biopsy: is there any value in examining biopsies at multiple levels? J Clin Pathol 2000;53:131-6.
13. Caroe A. Temporal artery biopsy to diagnose temporal arteritis [letter]. JAMA 1998;280:1992.